EPA Reviewer: Lisa Austin, Ph.D. **Signature:**
Registration Action Branch 1, Health Effects Division (7509C) **Date:** 7/30/09
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HED Executive Summary Cover for the attached OECD Formatted DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700b [§83-3b]; OECD 414.

PC CODE: 118203 **DP BARCODE:** D349929

TEST MATERIAL (PURITY): BAS 800 H (93.8%)

SYNONYMS: AC 433379; BASF Reg. No. 4054449, saflufenacil

CITATION: BAS 800 H Prenatal Developmental Toxicity Study in Himalayan Rabbits Oral Administration (Gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft 67056 Ludwigshafen, FGR. Laboratory report number: 40R0414/01173. Study report date: 08-February-2006. MRID 47128116. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, 26 Davis Drive, Research Triangle Park, NC 27709

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 47128116) BAS 800 H (93.8% a.i., batch/lot # COD - 000515) was administered to 25 female Crl:CHBB(HM) rabbits/dose by gavage at nominal dose levels of 0, 50, 200 or 600 mg/kg bw/day from days 6 through 28 of gestation.

There was an increase in maternal mortality at 600 mg/kg bw/d with an increase in does found dead, sacrificed *in extremis* or sacrificed following abortion. Clinical signs consisted of lateral position, poor general state, abortion, blood in bedding, discoloured or no urination and no or reduced defecation at 600 mg/kg bw/d. At the same dose, food consumption was decreased (8%), though there was no effect on body weight or body weight gain. At necropsy, there were increases (1-3/17-23 dams) in stomach ulceration and no faeces in the intestines at doses ≥ 200 mg/kg bw/d and in pale livers and kidneys, empty stomachs and enlarged bladders (1-3/17) at 600 mg/kg bw/d. Platelet counts were significantly decreased (12%) at 600 mg/kg bw/d, serum gamma glutamyl transferase activity was significantly decreased (19-20%), and triglycerides were increased (13-20%) at doses ≥ 200 mg/kg bw/d. Total bilirubins were increased (6-11%) and total liver porphyrins were increased (5-28-fold) at doses ≥50 mg/kg bw/d. These changes were not considered to be adverse. There were no treatment-related adverse changes in organ weight. Gravid uterine weights were decreased (8%) at 600 mg/kg bw/d along with decreased corpora lutea (10%), implantations (10%), live foetuses (11%) and litters (32%). **The maternal LOAEL was 600 mg/kg bw/d due to mortality and increased necropsy findings. The**

NOAEL was 200 mg/kg bw/d.

The only effect on foetal development was an increase in liver porphyrins at 200 mg/kg bw/d.

The developmental LOAEL is 200 mg/kg bw/day, based on increased liver porphyrins. The developmental NOAEL is 50 mg/kg bw/day.

The developmental toxicity study in the rabbit is classified acceptable,guideline and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

This Executive Summary was prepared for the United States Environmental Protection Agency, Office of Pesticide Program, Health Effects Division Use.

Much of the text was generated by the submitter(s) in OECD format. However, this document has undergone critical scientific analysis in comparison to the study report and modified as needed.

Reviewer #: 1755 , Date August 19, 2008

STUDY TYPE: Prenatal Developmental Study - Rabbit; OPPTS 870.3700; OECD 414.

TEST MATERIAL (PURITY): BAS 800 H (93.8% BAS 800 H)

SYNONYMS: AC 433379; BASF Reg. No. 4054449

Citation: PMRA 1547132. BAS 800 H Prenatal Developmental Toxicity Study in Himalayan Rabbits Oral Administration (Gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft 67056 Ludwigshafen, FGR. Laboratory report number: 40R0414/01173. Study report date: 08-February-2006. BASF Doc ID 2005/1029151. DACO 4.5.3

Sponsor: BASF Corporation, Agricultural Products, 26 Davis Drive, Research Triangle Park, NC 27709

MRID: Unavailable

EXECUTIVE SUMMARY:

In a developmental toxicity study, BAS 800 H (93.8% BAS 800 H) was administered 25 female Crl:CHBB(HM) rabbits/dose by gavage at dose levels of 0, 50, 200 or 600 mg/kg bw/day from days 6 through 28 of gestation.

There was an increase in maternal mortality at 600 mg/kg bw/d with an increase in does found dead, sacrificed *in extremis* or sacrificed following abortion. Clinical signs consisted of lateral position, poor general state, abortion, blood in bedding, discoloured or no urination and no or reduced defecation at 600 mg/kg bw/d. At the same dose, food consumption was decreased, though there was no effect on body weight or body weight gain. At necropsy, there were increases in stomach ulceration and no faeces in the intestines at doses ≥ 200 mg/kg bw/d and in pale livers and kidneys, empty stomachs and enlarged bladders. Platelet counts were decreased and total bilirubins were increased at 600 mg/kg bw/d. Gravid uterine weights were decreased at 600 mg/kg bw/d along with decreased absolute and relative corpora lutea, decreased absolute and relative implantations, decreased absolute and relative live foetuses and decreased litters. **The maternal LOAEL was 600 mg/kg bw/d due to increased mortality, decreased platelet counts and increased total bilirubin and increased necropsy findings. The NOAEL was 200 mg/kg bw/d.**

In foetal development, there was an increase in abortions at 600 mg/kg bw/d. **The**

10b

developmental LOAEL is 600 mg/kg bw/day, based on increased abortions. The developmental NOAEL is 200 mg/kg bw/day.

The developmental toxicity study in the rabbit is classified acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)

Description:	Solid / bright-beige
Lot/Batch #:	COD - 000515
Purity:	93.8 % BAS 800 H
Compound Stability:	The stability under the storage conditions present in this study was guaranteed by the Certificate of Analysis. The homogeneity of the test material in the dosing solution was confirmed by analysis.
CAS #:	372137-35-4

2. **Vehicle and/or positive control:** The test substance was given via gavage as an aqueous suspension in 1% Carboxymethylcellulose [CB 30.000].

3. **Test animals:**

Species:	Rabbit	
Strain:	Crl:CHBB(HM)	
Age/weight at study initiation:	Age: 18 – 21 weeks Weight: 2101 – 2833 g	
Source:	Charles River, Germany	
Housing:	12.2395.C stainless steel wire mesh cages supplied by Draht-Bremer GmbH (Marktheidenfeld, Germany); Floor area about 3,000 cm^2	
Diet:	Kliba maintenance diet for rabbits and guinea pigs "GLP", meal, supplied by Provimi Kliba SA, Kaiseraugst, Switzerland. *ad libitum*	
Water:	Tap water *ad libitum* in water bottles.	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	10/hr
	Photoperiod:	12hrs dark / 12hrs light
Acclimation period:	At least five days prior to test substance administration	

B. PROCEDURES AND STUDY DESIGN

1. **In life dates** - Start: February 3, 2005 End: March 17, 2005

2. **Mating:** The does were fertilized by means of artificial insemination. A synthetic hormone (0.2 mL of Receptal®) was injected intramuscularly to the female rabbits about one hour before insemination. The ejaculate samples used for the artificial insemination were derived from male Himalayan rabbits of the same breed as the females. Each female was inseminated with the sperm of a defined male donor. The male donors were kept under conditions (air conditioning, diet, water) comparable to those of the females participating in this study.

3. **Animal Assignment:** Animals were assigned to the different test groups according to a randomization plan (Nigenhuis and Wilf, 1978) taking into account their body weights.

TABLE 1: Animal Assignment

Dose (mg/kg bw/day)	0	50	200	600
# Females	25	25	25	25

4. Dose selection rationale: The low-dose (50 mg/kg bw/d) was the expected no adverse effect level. The intermediate dose level (200 mg/kg bw/d) was the dose level that could provide the opportunity for a gradation of toxic effects. The high-dose (600 mg/kg bw/day) was the dose level expected to induce some developmental and/or maternal toxicity but not death or severe suffering.

5. Dosage preparation and analysis - The aqueous test substance suspensions were prepared at the beginning of the administration period and thereafter at intervals, which took into account the analytical results of the stability verification.

For the preparation of the suspensions, an appropriate amount of the test substance was weighed depending on the dose group, in calibrated beakers and subsequently suspended in 1.0% Carboxymethylcellulose CB 30.000 in doubly distilled water using a high – speed homogenizer. A magnetic stirrer was used to keep the suspensions homogeneous during treatment of the animals. Test material-vehicle mixture was prepared at least every four days. The preparation was stored at room temperature for a maximum of four days.

Analytical verifications of the stability of the test substance in doubly distilled water for a period of at least 96 hours at room temperature were carried out before the study was initiated (in a similar batch). Samples of the test substance suspensions were sent to the analytical laboratory twice during the study period (at the beginning and towards the end) for verification of the concentrations.

The samples, which were taken for the first concentration control analyses at the beginning of the administration period, were also used to verify the homogeneity for the samples of the low and the high concentrations (50 and 600 mg/kg body weight/day). Three samples (one from the top, middle and bottom in each case) were taken for each of these concentrations from the beaker with a magnetic stirrer running.

Results - Homogeneity Analysis: For the low concentration preparation (0.5 g/100 mL), the mean concentration was 92.9% of the nominal concentration with a standard deviation of 2.4%. For the high concentration preparation (6 g/100 mL), the mean concentration was 98.3% of the nominal concentration with a standard deviation of 3.1%.

Stability Analysis: In doubly distilled water, the material was stable for a period of 96h (0 hr: 99.2% of nominal; 96hr: 99.0% of nominal).

Concentration Analysis: Mean concentrations were always greater than 90% and less

than 110% of the nominal concentrations.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** The test substance was administered to the animals orally (by gavage) in an ascending dose once a day from implantation to one day prior the expected day of parturition (days 6 - 28 p.i. (post insemination)) always at approximately the same time of day (in the morning). The animals of the control group were treated in the same way with the vehicle (1.0% Carboxymethylcellulose CB 30.000 in doubly distilled water). The volume administered each day was 10 mL/kg body weight. The calculation of the volume administered was based on the most recent individual body weight.

C. OBSERVATIONS

1. **Maternal Observations and Evaluations** - The animals were checked for mortality or clinical signs at least daily. Body weight data was recorded on days 0, 2, 4, 6, 9, 11, 14, 16, 19, 21, 23, 25, 28 and 29 p.i. . The consumption of food was determined daily during days 1 – 29 p.i. Dams were sacrificed on day 29 p.i.

Examinations at sacrifice consisted of the following:

Blood was taken by puncturing the ear vein from all surviving rabbits without anaesthesia. The rabbits were non-fasted. The blood sampling procedure and the subsequent analysis of the blood and serum samples were carried out in a randomized sequence. Liver samples were taken from five pregnant rabbits and their foetuses to determine liver porphyrins . The samples were stored at about –80°C until analysis.

Necropsy

On day 29 p.i., immediately after blood samples had been drawn, the surviving dams were sacrificed in randomized order by intravenous injection of pentobarbital. One low-dose, one mid-dose and seven high-dose group animals died or had to be sacrificed prematurely due to abortion or due to their moribund condition. The affected rabbits were examined according to the same procedures as the females killed on schedule (exception: no weight determinations of uterus, no blood or liver samplings).

After the dams had been sacrificed, they were necropsied and assessed by gross pathology in randomized order to minimize bias. Liver samples were taken from 5 pregnant rabbits/group to determine liver porphyrins. The uterus and the ovaries were removed and the following data were recorded:

- Weight of the liver and the spleen
- Weight of the unopened uterus
- Number of corpora lutea

- Number and distribution of implantation sites classified as:

• live foetuses
• dead implantations (early resorptions, late resorptions, dead foetuses)

Haematology

The following parameters were determined in blood with EDTA-K3 as anticoagulant using a particle counter.

- leukocytes (WBC)
- erythrocytes (RBC)
- haemoglobin (HGB)
- haematocrit (HCT)
- mean corpuscular volume (MCV)
- mean corpuscular haemoglobin (MCH)
- mean corpuscular haemoglobin concentration (MCHC)
- platelets (PLT)
- differential blood count
- reticulocytes

In addition, differential blood smears were prepared and stained according to Wright without being evaluated.

Clinical Chemistry

The following parameters were determined:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase (ALP)
- Serum-γ-glutamyltransferase (GGT)
- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Inorganic phosphate (INP)
- Calcium (Ca)
- Urea (UREA)
- Creatinine (CREA)
- Glucose (GLUC)
- Total bilirubin (TBIL)
- Total protein (TPROT)
- Albumin (ALB)
- Globulins (GLOB)
- Triglycerides (TRIG)

- Cholesterol (CHOL)
- Magnesium (Mg)
- Total porphyrin in liver tissue (LTPOR); from 10 randomly selected pregnant animals/group.

2. **Foetal Evaluations** - At necropsy, each foetus was weighed, sexed and examined macroscopically for any external findings. The viability of the foetuses and the condition of the placenta, the umbilical cords, the foetal membranes and fluids was examined. Individual placental weights were recorded. Thereafter, the foetuses were sacrificed by subcutaneous injection of a pentobarbital solution.

Soft tissue examination

After the foetuses had been sacrificed, the abdomen and thorax were opened in order to be able to examine the organs *in situ* before they were removed. The heart and the kidneys were sectioned in order to assess the internal structure. Liver samples were taken from the foetuses of five pregnant rabbits/group to determine liver porphyrins. The sex of the foetuses was determined by internal examination of the gonads.

After these examinations, the heads of approximately one half of the foetuses per dam (and the heads of those foetuses, which revealed severe findings (e.g. anophthalmia, microphthalmia or hydrocephalus) already during the external examination) were severed from the trunk. These heads were fixed in BOUIN's solution and processed and assessed according to WILSON's method subsequently (Wilson and Warkany, 1965). About ten transverse sections were prepared per head. After the examination the heads treated in this way were discarded. After skinning, all foetuses (including those without heads) were fixed in ethyl alcohol.

After fixation for approx. 1 - 5 days, the foetuses were removed from the fixative for a short while and a cross section of the heads from all intact foetuses was made in the parietal bone area using a scalpel. The two halves of the heads were carefully bent to allow a thorough examination of the brain. Subsequently, the foetuses were placed back into the fixative for further fixation.

Skeletal examination

After fixation in ethyl alcohol the skeletons (with the possible exception of the skulls) were stained according to a modified method of KIMMEL and TRAMMELL (Kimmel, C.A. and Trammell C., 1981). The stained skeletons were placed on an illuminated plate and examined, evaluated and assessed. After the examination, the stained skeletons were retained individually.

Evaluation Criteria for assessing the foetus

Malformation: A permanent structural change that is likely to adversely affect the survival or health.

Variation: A change that occurs also in foetuses of control animals and is unlikely to adversely affect the survival or health. This includes delays in growth or morphogenesis that has otherwise followed a normal pattern of development.

Unclassified observation: This term was used for those foetal findings, which could not be classified as malformations or variations (e.g. focal liver necrosis in foetuses). According to the definitions specified before, the findings obtained in foetuses were classified and listed in the tables accordingly.

D. DATA ANALYSIS

1. Statistical analyses:

Parameter	Statistical Test*	References
Food consumption, body weight, body weight change, corrected body weight gain (net maternal body weight change), carcass weight, weight of unopened uterus, number of corpora lutea, number of implantations, number of resorptions, number of live foetuses, proportions of preimplantation loss, proportions of postimplantation loss, proportions of resorptions, proportion of live foetuses in each litter, litter mean foetal body weight, litter mean placental weight	Simultaneous comparison of all dose groups with the control group using the DUNNETT-test (two-sided) for the hypothesis of equal means	DUNNETT, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096 - 1121 DUNNETT, C.W. (1964). New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482 - 491
Liver and spleen weights	Non-parametric one-way analysis using KRUSKALWALLIS- test (two-sided). If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using the WILCOXON-test (two-sided) for the equal medians	MILLER, R. G. (1981): Simultaneous Statistical Inference Springer-Verlag New York Inc., 165-167. International Mathematical and Statistical Libraries, Inc., 2500 Park West Tower One, Houston, Texas 77042-3020, USA, nakl-1 - nakl-3. NIJENHUIS, A. and WILF H.S. (1978): Combinatorial Algorithms, Academic Press, New York, 32-33. HETTMANNSPERGER, T. P. (1984): Statistical Inference based on Ranks, John Wiley & Sons New York, 132- 140.
Female mortality, females pregnant at terminal sacrifice, number of litters with foetal findings	Pair wise comparison of each dose group with the control group using FISHER'S EXACT test (one-sided) for the hypothesis of equal proportions	Siegel S. (1956): Non-parametric statistics for behavioural sciences. McGraw-Hill New York
Proportions of foetuses with malformations, variations and/or unclassified observations in each litter	Pair wise comparison of each dose group with the control group using the WILCOXON test (one-sided) for the hypothesis of equal medians	Nijenhuis, A.; Wilf H.S. (1978): Combinatorial Algorithms. Academic Press New York, 32-33 Hettmansperger, T. P. (1984); Statistical Inference based on Ranks. John Wiley & Sons

Parameter	Statistical Test*	References
		New York, 132-142
Clinical pathology parameters, Except reticulocytes and differential blood count	Non-parametric one-way analysis using KRUSKAL-WALLIS test (two-sided).If the resulting p-value was equal or less than 0.05, a pair-wise comparison of each dose group with the control group was performed using Wilcoxon-test (two-sided) for the equal medians	Siegel S. (1956): Non-parametric statistics for behavioural sciences. McGraw-Hill New York

2. **Indices:** The following indices were calculated from caesarean section records of animals in the study:

Implantation losses were classified as one of the following:

a) Early resorptions (only decidual or placental tissues visible or according to SALEWSKI (Salewski, 1964) from uteri from apparently non-pregnant animals and the empty uterus horn in the case of single-horn pregnancy)
b) Late resorptions (embryonic or fetal tissue in addition to placental tissue visible)
c) Dead fetuses (hypoxemic fetuses which did not breathe spontaneously after the uterus had been opened)

Calculations of conception rate and pre and post-implantation losses were determined according to the following formulas:

$$\text{Conception Rate (\%)} = \frac{\text{Number of pregnant animals}}{\text{Number of fertilized animals}} * 100$$

$$\text{Preimplantation Loss (\%)} = \frac{\text{Number of corpora lutea - Number of implantations}}{\text{Number of corpora lutea}} * 100$$

$$\text{Postimplantation Loss (\%)} = \frac{\text{Number of implantations - Number of live fetuses}}{\text{Number of implantations}} * 100$$

3. **Historical control data:** Historical control data from 2003 – 2004 (same source and strain, see page 302 of study report) were provided to allow comparison with concurrent controls in the analysis of foetal skeletal variations.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: The following observations were reported: Two high-dose dams were sacrificed in moribund condition on days 17 and 24, respectively. One dam from the 200 mg/kg bw/d dose group was found dead on GD 23 and one dam from the 600 mg/kg bw/d was found dead on GD 27. One 50 mg/kg bw/d dam was sacrificed following abortion on GD 23. Two 600 mg/kg bw/d dams were sacrificed following abortion on GD 24, another on GD25 and a final dam was sacrificed following abortion on GD 29 just prior to scheduled sacrifice. Clinical signs were limited to the 600 mg/kg bw/d dose group with lateral positioning, poor general state, abortion, blood in bedding, discoloured and no urination and reduced or no defecation. As such, increased mortality was considered to be treatment-related at 600 mg/kg bw/d.

Table 2. Dam Mortality [a]

Cause of Death	Dose in mg/kg bw/d			
	Control	50	200	600
Sacrificed moribund	0	0	0	**2**
Found dead	0	0	**1**	**1**
Sacrificed after abortion	0	**1**	0	**4**
Total Dead	0	**1**	**1**	**7**

[a] Data obtained from page 64 of the study report
Bolded values determined to be treatment-related

Table 2b. Select clinical signs in dams [a]

Clinical Sign	Dose in mg/kg bw/d			
	Control	50	200	600
Body position				
Lateral position	0	0	0	**1**
General state				
Poor general state	0	0	0	**2**
Miscellaneous				
Abortion	0	**1**	0	**4**
Blood in bedding	0	0	0	**3**
Stool/urine				
Urine, discoloured	0	0	0	**1**

No defecation	0	0	0	5
No urination	0	0	0	1
Reduced defecation	0	0	0	2

[a] Data obtained from pages 64 and 65 of the study report
Bolded values determined to be treatment-related

2. Body Weight – Body weight was comparable to controls. While there were a number of variations in body weight gain in gestating dams, there was no consistent pattern of decreased body weight gain in treated animals. Overall body weight gain was unchanged from concurrent controls. The weight of the gravid uterus was decreased at 600 mg/kg bw/d.

Table 3. Maternal Body Weight Gain (g)[a]

Interval	Dose in mg/kg bw/day			
	Control	50	200	600
Pretreatment: Days 0 – 2	27.6 ± 44.03 25[b]	27.8 ± 31.83 24	26.3 ± 34.75 24	24.3 ± 36.75 24
Days 4 – 6	0.8 ± 20.93 25	3.6 ± 20.27 24	4.8 ± 20.96 24	4.5 ± 18.25 24
Treatment: Days 6 – 9	-1.2 ± 27.13 25	10.7 ± 30.33 24	-15.7 ± 44.82 24	-14.6 ± 46.41 24
Days 9 – 11	17.3 ± 27.95 25	23.6 ± 19.59 24	35.5 ± 41.75 24	6.0 ± 42.34 24
Days 11 – 14	33.6 ± 38.38 25	37.6 ± 25.58 24	29.6 ± 41.87 24	39.1 ± 37.33 24
Days 14 – 16	57.7 ± 30.75 25	51.5 ± 32.37 24	47.8 ± 44.74 24	45.2 ± 49.39 24
Days 16 – 19	3.0 ± 38.54 25	-6.9 ± 32.32 24	3.6 ± 40.84 24	-11.1 ± 52.51 23
Days 19 – 21	-8.5 ± 39.87 25	-9.7 ± 27.24 24	-7.3 ± 48.25 24	2.9 ± 33.35 23
Days 21 – 23	21.3 ± 31.87 25	12.3 ± 45.71 24	17.4 ± 33.49 23	13.6 ± 33.53 23
Days 23 – 25	50.0 ± 30.58 25	49.0 ± 20.80 23	49.4 ± 27.92 23	48.5 ± 35.80 19
Days 25 – 28	55.9 ± 33.03 25	45.8 ± 28.61 23	56.1 ± 31.63 23	39.4 ± 56.68 18

Posttreatment:	22.0 ± 27.80	18.1 ± 25.95	7.4 ± 27.27	8.2 ± 30.54
Days 28 - 29	25	23	23	17
Pretreatment:	43.6 ± 52.44	24.0 ± 43.54	49.9 ± 49.21	39.5 ± 53.45
Days 0 – 6	25	24	24	24
Treatment:	229.1 ± 107.72	222.7 ± 75.17	217.9 ± 104.23	223.1 ± 84.31
Days 6 – 28	25	23	23	18
Days 0 - 29	294.7 ± 124.94	266.3 ± 85.90	276.3 ± 116.41	291.0 ± 94.03
	25	23	23	17
Gravid Uterus	339.9 ± 99.00	357.0 ± 45.10	335.0 ± 98.88	**312.6 ± 47.73 (↓8.03)**
	25	23	23	17
Carcass	2494.4 ± 158.26	2454.1 ± 142.10	2483.4 ± 169.12	2472.0 ± 174.06
	25	23	23	17
Net weight change from day 6	-88.8 ± 101.90	-116.2 ± 79.48	-109.7 ± 99.19	-68.1 ± 74.75
	25	23	23	17

[a] Data extracted from pgs 72 – 75 of the study report
[b] N
* Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control.

3. **Food Consumption** - Food consumption data are summarized as follows: Food consumption was decreased in the 600 mg/kg bw/d dose group from GD 6 – 18. Overall food consumption was decreased in the 600 mg/kg bw/d dose group.

Table 4. Maternal food consumption [a]

	Dose in mg/kg bw/day			
Interval	**Control**	**50**	**200**	**600**
Pretreatment:	100.7 ± 26.76	105.0 ± 21.73	107.0 ± 23.59	102.1 ± 20.10
Days 0 – 1	25[b]	24	24	24
Days 3 – 4	110.0 ± 15.99	101.8 ± 14.37	113.47 ± 17.43	106.6 ± 24.25
	25	24	24	24
Days 5 – 6	102.0 ± 18.23	99.4 ± 19.47	110.0 ± 22.8	99.2 ± 20.11
	25	24	24	24
Treatment:	96.1 ± 16.73	96.4 ± 19.06	99.3 ± 16.29	**78.5 ± 34.00* (↓18.31)**
Days 6 – 7	25	24	24	24

Days 7 – 8	96.4 ± 14.74 25	96.1 ± 22.20 24	96.7 ± 19.20 24	79.2 ± 34.80* (↓17.84) 24
Days 9 – 10	102.1 ± 13.71 25	101.8 ± 16.23 24	103.1 ± 20.53 24	94.3 ± 32.05 (↓7.64) 24
Days 11 – 12	99.2 ± 16.74 25	95.5 ± 15.71 24	100.7 ± 22.60 24	90.5 ± 32.10 (↓8.77) 24
Days 13 – 14	85.5 ± 21.06 25	81.2 ± 21.15 24	87.8 ± 24.06 24	78.2 ± 29.44 (↓8.54) 24
Days 15 – 16	83.4 ±2 8.07 25	80.7 ± 25.33 24	77.0 ± 30.48 24	67.5 ± 43.90 (↓19.06) 24
Days 17 – 18	86.9 ± 22.34 25	84.7 ± 19.44 24	89.5 ± 25.62 24	78.7 ± 36.18 (↓9.44) 23
Days 19 – 20	79.6 ± 18.84 25	68.9 ± 26.99 24	80.2 ± 27.44 24	76.8 ± 34.49 23
Days 21 – 22	76.5 ± 23.27 25	65.7 ± 27.53 24	79.0 ± 30.95 24	76.7 ± 39.05 23
Days 24 – 25	80.1 ± 16.87 25	71.0 ± 19.31 23	75.7 ± 24.24 23	80.4 ± 22.24 19
Days 25 – 26	84.0 ± 18.92 25	70.0 ± 23.25 23	76.3 ± 23.38 23	78.4 ± 22.20 19
Days 27 – 28	90.1 ± 19.85 25	75.2 ± 22.50* 23	80.0 ± 19.68 23	82.4 ± 19.16 18
Posttreatment: **Days 28 - 29**	90.5 ± 20.31 25	79.4 ± 17.70 23	76.3 ± 17.45* 23	81.5 ± 18.41 17
Pretreatment: **Days 0 – 6**	106.1 ± 4.24 6	103.0 ± 2.46 6	111.1 ± 2.86 6	104.8 ± 3.57 6
Treatment: **Days 6 – 28**	86.9 ± 10.02 22	81.4 ± 12.82 22	86.9 ± 10.33 22	79.4 ± 7.42 (↓8.63) 22
Days 6 - 29	87.0 ± 9.82 23	81.3 ± 12.53 23	86.5 ± 10.33 23	79.5 ± 7.27 (↓8.62) 23

[a] Data extracted from pgs 66 - 69 of the study report

[b] N
* Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control.
( ) represents percent change from control
Bolded values determined to be treatment-related

4. Gross Pathology - There were no treatment-related, adverse organ weight changes. At doses ≥ 200 mg/kg bw/d, there were stomach ulcerations, lack of faeces and assorted findings on implantations in dams sacrificed moribund. At 600 mg/kg bw/d, there was an increase in pale livers and kidneys, empty stomachs, enlarged bladders and assorted findings on implantations in dams which aborted.

Table 5a. Maternal organ weights [a]

	Dose in mg/kg bw/day (# of Dams)			
Organ weight (g)	Control (25)	50 (23)	200 (23)	600 (17)
Final body weight	2834 ± 169.9	2811 ± 145.5	2818 ± 185.8	2785 ± 190.2
Liver	60.42 ± 8.755	57.37 ± 8.278	57.76 ± 10.445	59.48 ± 8.444
Spleen	0.692 ± 0.1175	0.661 ± 0.1384	0.697 ± 0.1347	0.654 ± 0.1269

[a] Data obtained from page 76 of the study report.

Table 5b. Maternal gross necropsy findings [a]

	Dose in mg/kg bw/day (# of Dams)			
Finding	Control (25)	50 (23)	200 (23)	600 (17)
Liver: pale	0	0	0	2
Stomach: ulceration(s)	0	0	1	1
Stomach: empty	0	0	0	3
Kidney: pale	0	0	0	1
Intestines: no faeces	0	0	1	3
Bladder: enlarged	0	0	0	1
Dams sac. morb./died interc.	0	0	1	3
Size of implantations not according to day of pregnancy	0	0	1	0
All foetuses macerated	0	0	0	1
All foetuses resorbed	0	0	0	2
Dams with abortions	0	1	0	4
Size of implantations not according to day of pregnancy	0	1	0	2
Size of fetuses according to day of	0	0	0	1

preganancy				
Foetus with exencephaly	0	0	0	1
All fetuses macerated	0	0	0	1

[a] Data obtained from pages 78 and 79 of the study report
Bolded values determined to be treatment-related

5. Haematology and Clinical Chemistry – In haematological analysis, platelet counts were decreased in 600 mg/kg bw/d does. Serum gamma glutamyl transferase (SGGT) activity was decreased in all treated groups, total bilirubin was increased in 600 mg/kg bw/d doses, triglycerides were increased in 200 mg/kg bw/d doses and liver porphyrins were increased in all treated animals. The SGGT and liver porphyrin changes were not considered to be treatment-related, adverse as there were no other clinical, haematology or clinical chemistry changes at doses ≤ 200 mg/kg bw/d. The changes in triglycerides were not considered to be treatment-related, adverse due to the small nature of the change and the lack of dose-response. The findings are summarized in Tables 6a and 6b.

Table 6a. Select maternal haematology findings [a]

Parameter	Dose in mg/kg bw/day (# of Dams)			
	Control (25)	50 (23)	200 (23)	600 (17)
WBC (giga/L)	4.88 ± 1.25	5.56 ± 1.57 (↑13.9)	6.29 ± 1.72 (↑28.9)	6.28 ± 1.85** (↑28.7)
HCT (L/L)	0.356 ± 0.017	0.357 ± 0.018 (↑0.3)	0.362 ± 0.026 (↑1.7)	0.363 ± 0.029 (↑2.0)
MCHC (mmol/L)	20.67 ± 0.36	20.67 ± 0.33 (0.0)	20.66 ± 0.41 (↓0.04)	20.46 ± 0.44 (↓1.0)
PLT (giga/L)	388 ± 75	386 ± 60 (↓0.5)	401 ± 67 (↑3.4)	340 ± 66* (↓12.4)
MONO (%)	4.7 ± 1.5	4.1 ± 0.8 (↓12.8)	4.3 ± 1.1 (↓8.5)	3.9 ± 1.3 (↓17.0)
LUC (%)	1.5 ± 0.6	1.7 ± 0.8 (↑13.3)	1.8 ± 1.0 (↑20.0)	1.3 ± 0.7 (↓13.3)

[a] Data obtained from pages 83 and 84 of the study report
( ) represents percent change from control
Bolded values determined to be treatment-related

Table 6b. Select maternal clinical chemistry findings [a]

Parameter	Dose in mg/kg bw/day (# of Dams)			
	Control (25)	50 (23)	200 (23)	600 (17)
SGGT (nkat/L)	101 ± 22	90 ± 19 (↓10.9)	82 ± 21** (↓18.8)	81 ± 16** (↓19.8)
TBIL (µmol/L)	1.41 ± 0.30	1.52 ± 0.31 (↑7.8)	1.50 ± 0.22 (↑6.4)	1.57 ± 0.38 (↑11.3)
TRIG (mmol/L)	0.30 ± 0.11	0.30 ± 0.08 (0.0)	0.34 ± 0.09 (↑13.3)	0.36 ± 0.08 (↑20.0)
LTPOR (pmol/g P.)	69.0 ± 11.1	328.0 ± 76.5**	1008.4 ± 318.5**	1915.1 ± 839.2**

		(↑375.4)	(↑1361.4)	(↑2675.5)

[a] Data obtained from pages 86 – 89 of the study report
Bolded values were determined to be treatment-related

6. Caesarean Section Data - There was a treatment-related increase in maternal wastage at 600 mg/kg bw/d with increases in dams that were found dead, sacrificed moribund and an increase in abortions. At 600 mg/kg bw/d, there was also a decrease in total litters and total live foetuses and live foetuses/dam. There were no effects on resorptions, foetal body weights, sex ratios or postimplantation loss. There were decreases in the total corpora lutea and corpora lutea/dam, total implantations and implantations/dam at 600 mg/kg bw/d, but as treatment did not commence until after implantation, the change is not treatment-related. The findings are summarized in Table 7.

TABLE 7. Caesarean Section Observations [a]

Observation	Dose (mg/kg bw/day)			
	0	50	200	600
# Animals Assigned (Mated)	25	25	25	25
# Animals Pregnant	25	24	24	24
Pregnancy Rate (%)	100	96	96	96
# Nonpregnant	0	1	1	1
Maternal Wastage				
# Died[b]	0	1	1	7**
# Died Pregnant	0	1	1	7
# Died Nonpregnant	0	0	0	0
# Aborted	0	1	0	4
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	204	186 (↓8.8)	185 (↓9.3)	126 (↓38.2)
Corpora Lutea/Dam	8.2 ± 1.60	8.1 ± 1.35 (↓1.2)	8.0 ± 1.55 (↓2.4)	7.4 ± 1.37 (↓9.8)
Total # Implantations	169	173 (↑2.4)	158 (↓6.5)	104 (↓38.9)
(Implantations/Dam)	6.8 ± 2.44	7.5 ± 1.08 (↑10.3)	6.9 ± 2.07 (↑1.5)	6.1 ± 1.41 (↓10.3)
Total # Litters	25	23 (↓8)	23 (↓8)	17** (↓32)
Total # Live Foetuses	157	162 (↑3.2)	150 (↓4.5)	96 (↓38.9)
(Live Foetuses/Dam)	6.3 ± 2.19	7.0 ± 1.02 (↑11.1)	6.5 ± 2.04 (↑3.2)	5.6 ± 1.11 (↓11.1)
Total # Dead Foetuses	2	0	0	0
(Dead Foetuses/Dam)				
Total # Resorptions	10	11	8	8
Early	7	7	6	8
Late	3	4	2	0
Resorptions/Dam	0.4 ± 0.58	0.5 ± 0.67	0.3 ± 0.49	0.5 ± 0.80
Early	0.3 ± 0.46	0.3 ± 0.56	0.3 ± 0.45	0.5 ± 0.80
Late	0.1 ± 0.33	0.2 ± 0.39	0.1 ± 0.29	0.0 ± 0.00
Litters with Total Resorptions	0	0	0	0
Mean Foetal Weight (g)	39.6 ± 4.43	37.1 ± 2.93 (↓6.3)	38.1 ± 6.65 (↓3.8)	39.7 ± 3.09 (↑0.3)
Males	39.8 ± 4.32	37.0 ± 3.57 (↓7.0)	37.9 ± 7.01 (↓4.8)	39.5 ± 2.72 (↓0.8)

Females	39.0 ± 4.71	36.9 ± 3.19 (↓5.4)	37.9 ± 5.71 (↓2.8)	39.3 ± 3.61 (↑0.8)
Sex Ratio (% Male)	50.3	42.0 (↓16.5)	51.3 (↑2.0)	46.9 (↓6.8)
Preimplantation Loss (%)	17.9 ± 24.23	6.4 ± 7.85 (↓64.2)	16.0 ± 18.57 (↓10.6)	16.9 ± 14.49 (↓5.6)
Postimplantation Loss (%)	5.8 ± 8.11	6.0 ± 8.26 (↑3.4)	5.0 ± 7.40 (↓13.8)	6.4 ± 9.92 (↑10.3)

[a] Data extracted from pgs 80 - 82 and 92 of the study report.
[b] Includes animals found dead, sacrificed moribund and sacrificed following abortion.
* Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control.

B. DEVELOPMENTAL TOXICITY

1. **Blood analyses** – Liver porphyrins were increased at doses ≥ 200 mg/kg bw/d in males and females. The nature of the changes to the total liver porphyrins was unclear due to a lack of haematological parameters measured in the study. However, in the dams porphyrins are increased at levels where there are no other adverse changes and, while treatment-related, the change is not indicative of toxicity. See Table 8.

Table 8a. Liver porphyrin levels in foetuses [a]

Parameter	Males			
	Dose in mg/kg bw/day (# of Foetuses)			
	Control (17)	50 (16)	200 (17)	600 (12)
LTPOR (pmol/g P.)	680.0 ± 223.3	588.9 ± 184.2 (↓13.4)	988.7 ± 422.1** (↑45.4)	1183.3 ± 467.8** (↑74.0)
Parameter	Females			
	Dose in mg/kg bw/day (# of Foetuses)			
	Control (19)	50 (19)	200 (14)	600 (13)
LTPOR (pmol/g P.)	598.3 ± 167.7	606.2 ± 212.5 (↑1.3)	787.3 ± 276.2* (↑31.6)	1247.9 ± 324.8** (↑108.6)

[a] Data extracted from pgs 90 - 91 of the study report.
* Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control.
Bolded values were determined to be treatment-related

2. **External Examination** – There were no treatment-related changes observed in the external examinations. See Table 8b.

3. **Visceral Examination** – There were no treatment-related changes to visceral malformations. There was one 600 mg/kg bw/d foetus with multiple visceral malformations, however, this was determined to be a result of variability and not treatment-related. While the number of foetuses with an absent lung lobe was slightly increased, the proportion of litters with the finding was not and the finding was not determined to be treatment-related. See Table 8c.

4. **Skeletal Examination** – There was a slight increase in the number of litters with skeletal malformations at doses ≥ 200 mg/kg bw/d, especially when considering the reduced litters at 600

mg/kg bw/d. At 200 mg/kg bw/d, there was one foetus with sternebrae fused into a bony plate and one foetus with broken sternebra, ribs, humerus, tibia and fibula and knobby ulna and rib. At 600 mg/kg bw/d, there was one foetus with small interparietal and supraoccipital bones and another foetus with lumbar hemivertebra. However, since these were single incidences and there were no patterns of malformation and no changes to the number of variations or unclassified changes, these malformations were not considered to be treatment-related. See Table 8d.

TABLE 8b. External Examinations [a]

Observations+	Dose (mg/kg bw/day)			
	0	50	200	600
#Foetuses(litters) examined	159 (25)[b]	162 (23)	150 (23)	96 (17)
Variation				
#Foetuses(litters) affected	5 (3)	3 (3)	4 (3)	2 (2)
Paw hyperflexion	5 (3)	3 (3)	4 (3)	2 (2)

+Some observations may be grouped together
[a]Data extracted from pgs 93 - 95 of the study report.
[b]Foetal (litter) incidence
* Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control.

TABLE 8c. Visceral Examinations [a]

Observations+	Dose (mg/kg bw/day)			
	0	5	20	60
#Foetuses(litters) examined	159 (25)[b]	162 (23)	150 (23)	96 (17)
Malformation				
#Foetuses(litters) affected	1 (1)	4 (3)	4 (2)	1 (1)[c]
Heart: Muscular ventricular septum defect	0 (0)	2 (2)	1 (1)	0 (0)
Absent uterine horn (right)	0 (0)	0 (0)	0 (0)	1 (1)
Absent ovary (right)	0 (0)	0 (0)	0 (0)	1 (1)
Absent (right)	0 (0)	0 (0)	0 (0)	1 (1)
Absent ureter (right)	0 (0)	0 (0)	0 (0)	1 (1)
Diaphragmatic hernia	0 (0)	0 (0)	0 (0)	1 (1)
Variation				
#Foetuses(litters) affected	17 (10)	9 (5)	16 (9)	13 (5)
Absent lung lobe (L. inferior medialis)	10 (7)	5 (2)	10 (7)	12 (4)

+Some observations may be grouped together
[a]Data extracted from pgs 99 - 103 of the study report.
[b]Foetal (litter) incidence
[c] One foetus with multiple visceral malformations
* Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control.

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TABLE 8d. Skeletal Examinations [a]

Observations+	Dose (mg/kg bw/day)			
	0	5	20	60
#Foetuses(litters) examined	159 (25)	162 (23)	150 (23)	96 (17)
Malformation				
#Foetuses(litters) affected	1 (1)	0 (0)	2 (2)	2 (2)
Foetuses with multiple skeletal malformations	0 (0)	0 (0)	1 (1) [0.6 (4.3)]	1 (1) [1.0 (5.9)]
HC: Foetuses with multiple skeletal malformations	0.0 – 0.8 (0.0 – 4.3)			
Small interparietal	0 (0)	0 (0)	0 (0)	1 (1)[c]
Small supraoccipital	0 (0)	0 (0)	0 (0)	1 (1)[c]
Lumbar hemivertebra	0 (0)	0 (0)	0 (0)	1 (1)
Sternebrae severely fused (bony plate); unchanged cartilage	0 (0)	0 (0)	1 (1)	0 (0)
Broken sternebra; unchanged cartilage	0 (0)	0 (0)	1 (1)[d]	0 (0)
Knobby rib	0 (0)	0 (0)	1 (1)[d]	0 (0)
Broken rib	0 (0)	0 (0)	1 (1)[d]	0 (0)
Broken humerus	0 (0)	0 (0)	1 (1)[d]	0 (0)
Knobby ulna	0 (0)	0 (0)	1 (1)[d]	0 (0)
Broken tibia	0 (0)	0 (0)	1 (1)[d]	0 (0)
Broken fibula	0 (0)	0 (0)	1 (1)[d]	0 (0)
Variation				
#Foetuses(litters) affected	103 (25)	103 (22)	102 (23)	58 (14)
Supernumerary thoracic vertebra	0 (0)	0 (0)	0 (0)	1 (1)
Supernumerary rib (13th); cartilage not present	4 (4)	7 (6)	2 (1)	5 (3)
Cervical rib; cartilage present	0 (0)	0 (0)	0 (0)	1 (1)
Unclassified				
#Foetuses(litters) affected	54 (20)	52 (19)	50 (17)	29 (11)
Notched manubrium	0 (0)	0 (0)	0 (0)	1 (1)

+Some observations may be grouped together
[a] Data extracted from pgs 104 – 120 of the study report.
[b] Foetal (litter) incidence
[c] Indicated changes occurred in one high-dose foetus
[d] Indicated changes occurred in one mid-dose foetus
* Significantly different ($p < 0.05$) from the control; ** Significantly different ($p < 0.01$) from the control.

III. DISCUSSION

A. Investigators' conclusions:

"**BAS 800 H** was administered to pregnant Himalayan rabbits daily by stomach tube from implantation to one day prior to the expected day of parturition (days 6 - 28 p.i.).

Substance-related, signs of **maternal toxicity** were exclusively observed at the high dose level, i.e. 600 mg/kg body weight/day. 2 high dose dams (Nos. 79 and 99) had to be killed before schedule due to their poor general condition. One high dose female (No. 87) was found dead on day 27 p.i.. Moreover, 4 high dose rabbits (Nos. 77, 83, 91 and 92) aborted and were consequently sacrificed before schedule. Most of these does showed adverse accompanying clinical (e.g. urine discolored, no/reduced defecation/urination, lateral position, poor general state, blood in bedding) and gross necropsy findings (e.g. empty stomach/intestines, stomach ulcerations, pale liver or kidneys). Food consumption of the 600 mg/kg rabbits was statistically significantly impaired (up to 18%) at initiation of treatment (days 6 – 8 p.i.) and about 9% below controls if calculated for the entire treatment phase (days 6 - 28 p.i.). Body weight, absolute and corrected body weight change as well as uterine, liver and spleen weights, however, were comparable between the high dose rabbits and the control group.

There occurred no substance-induced effects in the low and the mid dose rabbits (50 or 200 mg/kg body weight/day) on general clinical condition, food consumption, body and organ weights and during gross necropsy examinations. The occurrence of abortion in one low dose rabbit (No. 33) and of premature death in one mid dose animal (No. 57) is assessed to be spontaneous in nature and not substance-related. Spontaneous abortions or deaths in single does are not uncommon findings in the strain of rabbits used for this study.

Regarding clinical pathology, no treatment-related changes were observed in the haematological and clinical chemical examinations of the dams. However, marked, dose-dependent increases in porphyrin concentration were measured in the liver homogenates of the treated dams. These effects originated from the mode of action of the test compound. BAS 800 H acts as a protoporphyrinogen IX oxidase inhibitor. Protoporphyrinogen IX oxidase is the penultimate enzyme in the heme biosynthesis. Inhibition of protoporphyrinogen IX oxidase inhibits the formation of heme and causes an accumulation of porphyrins. Based on their solubility, various porphyrins preferentially accumulate in plasma and tissues and are excreted in either urine or feces. Porphyrin accumulation can cause a variety of secondary toxicological effects (e.g. sideroblastic anemia and indications for liver toxicity). However, such findings did not occur in the present prenatal developmental toxicity study with pregnant rabbits and it is questionable if there is an interrelationship between the increases in liver porphyrin concentration at the 600 mg/kg group and the adverse clinical and necropsy findings, which were observed at this dose level.

There were no differences of toxicological relevance between the control and the substance-treated groups (50; 200 and 600 mg/kg body weight/day) in conception rate, mean number of

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corpora lutea, total implantations, resorptions and live fetuses, fetal sex ratio or in the values calculated for the pre- and the postimplantation losses.

No substance-related differences were recorded for placental and fetal body weights. The external, soft tissue and skeletal examinations of the fetuses revealed no differences between the control and the substance-treated groups, which might be related to the test substance. Number and type of fetal external, soft tissue and skeletal findings, which were classified as malformations and/or variations, did not show any differences of toxicological relevance between the groups. Liver porphyrins were marginally, but statistically significantly increased in the mid and high dose male and female fetuses (200 and 600 mg/kg body weight/day) and in the dams of all dose groups (see above). As such, it is concluded that the fetuses are less susceptible to the enzyme inhibitory effects of BAS 800 H than are the does.

Thus, under the conditions of this full-scale study, the administration **of BAS 800 H** to pregnant female Himalayan rabbits by stomach tube at a dose level of 600 mg/kg body weight/day elicited **distinct signs of maternal toxicity**, but was not maternally toxic at dose levels 50 and 200 mg/kg body weight/day. The increase in the does' liver porphyrins at 50 and 200 mg/kg in the absence of any other substance-related effects is not considered as toxicologically significant.

The test substance administration up to and including 600 mg/kg body weight/day had **no influence on gestational parameters and induced no signs of prenatal developmental toxicity**; especially, there were **no indications of teratogenic effects** which could be causally related to the test substance. The marginal increases in liver porphyrins of the mid and high dose male and female fetuses (200 and 600 mg/kg body weight/day) in the absence of any other substance-related effects on the progeny are also not considered as toxicologically significant.

Based on the results of this prenatal developmental toxicity study, the **no observed adverse effect level (NOAEL)** for **maternal toxicity** is **200 mg/kg body weight/day**, while it is **600 mg/kg body weight/day** for **prenatal developmental toxicity.** Due to increases in liver porphyrins, the **no observed effect level (NOEL)** for the **maternal organism** is **below 50 mg/kg body weight/day**, while it is **50 mg/kg body weight/day** for the **fetuses**."

B. Reviewer's discussion:

1. Maternal toxicity: There was an increase in doe mortality at 600 mg/kg bw/d, with animals sacrificed, found dead and sacrificed following abortions. At 600 mg/kg bw/d, there was an increase in clinical signs consisting of lateral position, poor general state, abortion, blood in bedding, discoloured and no urination and no and reduced defecation. Gravid uterine weights were reduced compared to control and food consumption was decreased throughout the treatment period, though there was no effect on body weight or body weight gain. At necropsy, 200 mg/kg bw/d does were found to have single animal increases in stomach ulceration and no faeces in intestines. At 600 mg/kg bw/d there were increases in pale livers, stomach ulcerations, empty stomachs, pale kidneys, no faeces in the intestines and enlarged bladders. Platelet counts were decreased at 600 mg/kg bw/d. Total bilirubin was increased at 600 mg/kg bw/d. Caesarean

section observations revealed an increase in maternal wastage, decreased absolute and relative corpora lutea, decreased absolute and relative implantations, decreased absolute and relative live foetuses and decreased litters at 600 mg/kg bw/d. The maternal LOAEL was 600 mg/kg bw/d due to increased mortality, decreased platelet counts and increased total bilirubin and increased necropsy findings. The NOAEL was 200 mg/kg bw/d.

2. **Developmental toxicity:** The foetal LOAEL was 600 mg/kg bw/d based on increased abortions. The foetal NOAEL was 200 mg/kg bw/d.

a. Deaths/Resorptions: There was an increase in abortions at 600 mg/kg bw/d. There was no effect on resorptions.

b. Altered Growth: There was no effect on foetal growth.

c. Developmental Variations: There was no effect on developmental variations.

d. Malformations: There was no effect on foetal malformations.

C. Study deficiencies: There were no deficiencies that would affect the outcome of the study.

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